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Original Contribution

Serum and Dietary Magnesium and Risk of Ischemic Stroke

The Atherosclerosis Risk in Communities Study

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The authors sought to examine the relation between serum or dietary magnesium and the incidence of ischemic stroke among blacks and whites. Between 1987 and 1989, 14,221 men and women aged 45–64 years took part in the first examination of the Atherosclerosis Risk in Communities Study cohort. The incidence of stroke was ascertained from hospital records. Higher serum magnesium levels were associated with lower prevalence of hypertension and diabetes mellitus at baseline. During the 15-year follow-up, 577 ischemic strokes occurred. Serum magnesium was inversely associated with ischemic stroke incidence. The age-, sex-, and race-adjusted rate ratios of ischemic stroke for those with serum magnesium levels of $\leq$1.5, 1.6, 1.7, and $\geq$1.8 mEq/L were 1.0, 0.78 (95% confidence interval (CI): 0.62, 0.96), 0.70 (95% CI: 0.56, 0.88), and 0.75 (95% CI: 0.59, 0.95) ($P_{trend} = 0.005$). After adjustment for hypertension and diabetes, the rate ratios were attenuated to nonsignificant levels. Dietary magnesium intake was marginally inversely associated with the incidence of ischemic stroke ($P_{trend} = 0.09$). Low serum magnesium levels could be associated with increased risk of ischemic stroke, in part, via effects on hypertension and diabetes.

brain infarction; diet; magnesium; risk factors

Abbreviations: ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; CT, computerized tomography; HDL, high density lipoprotein; LDL, low density lipoprotein; MRI, magnetic resonance imaging; RR, rate ratio.

Magnesium is a natural calcium antagonist and modulates vasomotor tone, blood pressure, and peripheral blood flow. Previous epidemiologic studies have reported that magnesium intake or serum magnesium levels are inversely associated with cardiovascular risk factors such as hypertension (1, 2), type 2 diabetes mellitus (1, 3), and the metabolic syndrome (4). Therefore, low magnesium intake could increase the risk of stroke, especially ischemic stroke, but few prospective studies have reported the association of magnesium intake with the incidence of ischemic stroke (5, 6). The Nurses' Health Study reported that women in the highest quintile of dietary magnesium intake had a 21% lower risk of incidence of ischemic stroke compared with those in the lowest quintile (6), but the association was not statistically significant. The association of dietary magnesium intake with the incidence of ischemic stroke could be modified by other dietary minerals, such as calcium and potassium (6). Further, the association between dietary and serum magnesium is weak (1). Therefore, the mechanisms by which low levels of magnesium lead to risk of ischemic stroke may differ between dietary and serum magnesium, and examining both dietary and serum magnesium could provide further evidence on the association of magnesium with the incidence of ischemic stroke. For instance, the joint impact of high dietary magnesium intake and high serum magnesium levels on the incidence of ischemic stroke could be synergistic. No study, however, has reported such an association.

In the Atherosclerosis Risk in Communities (ARIC) Study, serum magnesium levels were inversely associated

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with the incidence of hypertension and diabetes mellitus, but dietary magnesium levels were not (3, 7). Further, another ARIC Study demonstrated that serum magnesium levels were inversely associated with the incidence of coronary heart disease, but dietary magnesium levels were not (8). Therefore, the associations between serum magnesium and the incidence of ischemic stroke could be hypothesized to be stronger than those between dietary magnesium and ischemic stroke. We further hypothesize that hypertension and diabetes mellitus are important factors mediating the association of serum magnesium with the incidence of ischemic stroke.

To examine the relation of serum and dietary magnesium with the incidence of ischemic stroke, we used data from follow-up of men and women in the ARIC Study.

MATERIALS AND METHODS

Study population

The ARIC Study cohort comprised 15,792 men and women aged 45–64 years between 1987 and 1989 in 4 US communities: Forsyth County, North Carolina; Jackson, Mississippi; 8 northwestern suburbs of Minneapolis, Minnesota; and Washington County, Maryland (9).

We excluded participants in Forsyth County who were not white or black ($n = 21$) and participants in Minneapolis and Washington County who were not white ($n = 82$). We then excluded participants with a history of stroke or transient ischemic attack at baseline ($n = 282$) and participants with missing data for serum or dietary magnesium ($n = 1,847$) at baseline. The remaining 13,560 participants (2,027 black women, 1,266 black men, 5,481 white women, and 4,786 white men) were followed to determine the incidence of stroke through 2004. The study protocol was approved by the institutional review boards of the collaborating institutions, and informed, written consent was obtained from each participant.

Baseline measurements

Methods for blood processing in the ARIC Study have been described (10). Participants were asked to fast for 12 hours before their morning clinic appointments. The measurement of serum magnesium was based on the procedure of Gindler and Heth and used the metallochromic dye, calmagite (1-(1-hydroxy-4-methyl-2-phenylazo)-2-napthol-4-sulfonic acid). The laboratory coefficient of variation, based on blinded split samples sent 1 week apart to the laboratory, was 3% (1), and repeated testing of 40 individuals over several weeks yielded a reliability coefficient of 0.69 (11). Plasma fibrinogen and the von Willebrand factor antigen were measured by the thrombin time titration method and enzyme-linked immunosorbent assay, respectively. Serum glucose was measured by a hexokinase/glucose-6-phosphate dehydrogenase method. Body mass index was calculated as weight (kg)/height $(m)^2$. We defined prevalent coronary heart disease and stroke at baseline, for exclusion, as a self-reported history of a physician-diagnosed heart attack, prior myocardial infarction by electrocardiogram, prior cardiovascular surgery, prior coronary angioplasty, or prior stroke or transient ischemic attack identified by a standardized interview (12).

Dietary information over the last year was collected by using Willett's 61-item food frequency questionnaire, adapted for interviewer administration and otherwise modified only slightly (13). Dietary magnesium intake was computed by multiplying the magnesium content of each food item by the frequency of its daily consumption and summing over all items. In the ARIC Study, serum magnesium was remeasured for 91% of the participants in 1990–1992, and dietary magnesium was remeasured for 82% in 1993–1995. The Spearman correlation coefficients between 2 visits were 0.45 for serum magnesium and 0.54 for dietary magnesium. The Spearman correlation coefficient between serum and dietary magnesium at baseline was 0.04.

Endpoint determination

For the present study, we included stroke events (9) occurring between ARIC Study visit 1 (1987–1989) and December 31, 2004. Transient ischemic attacks were not ascertained. All participants were contacted annually by phone, and all hospitalizations and deaths in the previous year were identified. We also surveyed lists of discharges from local hospitals and death certificates from state vital statistics offices for potential cerebrovascular events. Abstractors recorded signs and symptoms and photocopied neuroimaging (computerized tomography (CT) or magnetic resonance imaging (MRI)) and other diagnostic reports if the list of discharge diagnoses included a cerebrovascular disease code (*International Classification of Diseases*, Ninth Revision, codes 430–438), if a cerebrovascular condition or procedure was mentioned in the discharge summary, or if a cerebrovascular finding was noted on a CT or MRI report. Of the stroke-eligible hospitalizations through 1997, 84% had at least 1 CT scan, 27% had an MRI of the head, 15% had a cerebral angiography, and 6% had a lumbar puncture (14). Each eligible case was classified by computer algorithm and by expert reviewer, according to criteria adapted from the National Survey of Stroke (15). Details on quality assurance for ascertainment and classification of stroke are described elsewhere (14). Qualifying strokes were further classified into definite or probable hospitalized ischemic (cardioembolic or thrombotic) or hemorrhagic stroke on the basis of neuroimaging studies and autopsy, when available.

Statistical analysis

Differences among the quartiles of serum or dietary magnesium in age-, sex-, and race-adjusted mean values or prevalences of potential confounding factors at baseline were calculated by using analysis of variance or logistic regression models, and their trends were tested by using linear regression for continuous variables and logistic regression for dichotomous variables. Median values of the serum or dietary magnesium categories were used in these analyses.

The time at risk (time to event or time to censoring) was calculated from the date of the baseline examination to the earliest of the following: date of hospital admission for

Table 1. Age-, Sex-, and Race-adjusted Baseline Characteristics According to Serum Magnesium Levels, Atherosclerosis Risk in Communities Study, 1987–1989

	Quartiles of Serum Magnesium				P_{trend}
	1 (Low)	2	3	4 (High)	
No.	3,619	3,529	3,431	2,947	
Median, mEq/L	1.44	1.60	1.70	1.84	
Range, mEq/L	≤1.50	1.51–1.60	1.61–1.79	≥1.80	
Age, years[a]	54.2	54.0	54.2	54.3	0.40
Male, %[b]	41.5	45.6	45.5	46.3	<0.001
African Americans, %[c]	37.2	23.9	18.2	16.0	<0.001
Educational level (post-high school), %	39.8	44.8	44.9	47.6	<0.001
Body mass index, kg/m^2	28.1	27.3	27.2	26.9	<0.001
Systolic blood pressure, mm Hg	123	120	120	119	<0.001
Use of antihypertensive medication, %	36.6	27.7	25.4	24.0	<0.001
Current smoking, %	26.3	25.8	26.5	24.8	0.26
Diabetes mellitus, %	17.9	9.7	7.1	5.6	<0.001
Low density lipoprotein cholesterol, mg/mL	134	137	139	141	<0.001
High density lipoprotein cholesterol, mg/mL	51.0	52.2	52.8	52.8	<0.001
Fibrinogen, mg/dL	304	301	300	302	0.11
von Willebrand factor, %	123	117	115	113	<0.001
Alcohol intake, g/week of ethanol	44.3	39.2	44.0	43.8	0.92
Total energy intake, kcal/day	1,623	1,631	1,630	1,627	0.67
Dietary calcium intake, mg/day	655	658	662	655	0.80
Dietary potassium intake, mg/day	2,629	2,630	2,641	2,655	0.23
Dietary sodium intake, mg/day	1,478	1,483	1,483	1,476	0.96
Dietary magnesium intake, mg/day	251	253	255	258	0.004

[a] Adjusted for sex and race.
[b] Adjusted for age and race.
[c] Adjusted for age and sex.

incident stroke, date of death, date of last follow-up contact, or December 31, 2004. Because the number of hemorrhagic stroke cases was small ($n = 87$), we analyzed the associations of dietary or serum magnesium with the incidence of ischemic stroke only.

The rate ratios of ischemic stroke incidence and 95% confidence intervals relative to the lowest quartile of serum and dietary magnesium were calculated, with adjustment for age and other potential confounding factors, by using the Cox proportional hazards model. We selected covariates on the basis of previous prospective findings for ischemic stroke in the ARIC Study (16, 17). Covariates included age (years), sex, race-field center, smoking status (never, former, and current smokers), body mass index (kg/m^2), low density lipoprotein (LDL) cholesterol (mg/dL), high density lipoprotein (HDL) cholesterol (mg/dL), fibrinogen (mg/dL), von Willebrand factor (%), educational level (post-high school, high school or less), and total energy intake (kcal/day). Unfortunately, the ARIC Study did not have information on supplemental magnesium intake. Because we hypothesized that hypertension and diabetes could mediate the association between magnesium and ischemic stroke incidence, we included systolic blood pressure (mm Hg), antihypertensive medication use (yes, no), and diabetes status (yes, no) at baseline in a final model. We tested interactions between serum or dietary magnesium and sex, race, diuretic use, or diabetes status for ischemic stroke based on comparison of linear trends. Further, to quantify the relative contribution of hypertension and diabetes status to the observed association of magnesium with the incidence of ischemic stroke, we used the following formula: $(\text{rate ratio (RR)}_{\text{basic model}} - \text{RR}_{\text{adjusted model}})/(\text{RR}_{\text{basic model}} - 1) \times 100\%$ (18, 19). $\text{RR}_{\text{basic model}}$ represents the rate ratio for incidence of ischemic stroke adjusted for age, sex, and race, and $\text{RR}_{\text{adjusted model}}$ reflects the rate ratio for incidence of ischemic stroke with additional adjustment for systolic blood pressure, antihypertensive medication use, and diabetes status.

RESULTS

Table 1 shows age-, sex-, and race-adjusted mean values or prevalences of risk characteristics at baseline according to quartiles of serum magnesium. Systolic blood pressure, body mass index, and von Willebrand factor levels were inversely associated with serum magnesium levels, and LDL cholesterol and HDL cholesterol levels and dietary magnesium intake were greater with increasing serum

Table 2. Age-, Sex-, and Race-adjusted Baseline Characteristics According to Dietary Magnesium Levels, Atherosclerosis Risk in Communities Study, 1987–1989

	Quartiles of Magnesium Intake				P_{trend}
	1 (Low)	2	3	4 (High)	
No.	3,306	3,315	3,321	3,335	
Median, mg/day	152	213	271	362	
Range, mg/day	<186	186–241	242–307	>307	
Age, years[a]	53.9	54.4	54.1	54.2	0.20
Male, %[b]	37.4	41.7	45.0	54.3	<0.001
African Americans, %[c]	32.4	24.5	20.9	18.5	<0.001
Educational level (post-high school), %	38.0	43.8	46.5	48.8	<0.001
Body mass index, kg/m^2	27.3	27.3	27.4	27.5	0.25
Systolic blood pressure, mm Hg	121	121	121	120	0.02
Use of antihypertensive medication, %	29.7	29.5	28.4	27.4	0.02
Current smoking, %	26.1	25.0	24.7	27.2	0.23
Diabetes mellitus, %	10.1	10.3	9.6	11.0	0.22
Low density lipoprotein cholesterol, mg/mL	139	137	137	137	0.01
High density lipoprotein cholesterol, mg/mL	51.5	52.2	52.1	52.8	0.001
Fibrinogen, mg/dL	302	302	300	304	0.18
von Willebrand factor, %	118	118	115	117	0.55
Alcohol intake, g/week of ethanol	31.1	37.1	43.0	59.9	<0.001
Total energy intake, kcal/day	1,110	1,425	1,720	2,250	<0.001
Dietary calcium intake, mg/day	372	538	700	1,017	<0.001
Dietary potassium intake, mg/day	1,603	2,275	2,833	3,830	<0.001
Dietary sodium intake, mg/day	975	1,287	1,569	2,085	<0.001
Serum magnesium, mEq/L	1.63	1.63	1.64	1.64	0.02

[a] Adjusted for sex and race.
[b] Adjusted for age and race.
[c] Adjusted for age and sex.

magnesium levels. Higher serum magnesium levels were also associated with a lower prevalence of antihypertensive medication use, diuretic use, and diabetes mellitus. Alcohol intake, total energy intake, and dietary intake of calcium, potassium, and sodium were not associated with serum magnesium levels. As shown in Table 2, systolic blood pressure and LDL cholesterol levels were inversely associated with dietary magnesium intake, and HDL cholesterol levels, serum magnesium level, alcohol intake, total energy intake, and dietary calcium, potassium, and sodium intakes were positively associated with dietary magnesium intake.

Among the 13,560 men and women followed for an average of 15.0 years, 577 ischemic stroke cases occurred. Participants with serum magnesium levels of 1.7 mEq/L and ≥1.8 mEq/L had 30% and 25% lower age-, sex-, and race-adjusted rate ratios of ischemic stroke than did those with serum magnesium levels of ≤1.5 mEq/L, the rate ratio being 0.70 (95% confidence interval (CI): 0.56, 0.88) and 0.75 (95% CI: 0.59, 0.95) (Table 3) ($P_{trend} = 0.005$). The rate ratios were slightly attenuated by additional adjustment for body mass index, smoking status, LDL cholesterol, HDL cholesterol, fibrinogen, von Willebrand factor, and educational level, but they remained borderline significant ($P_{trend} = 0.05$). However, further adjustment for other risk factors that could be mediators between magnesium and ischemic stroke—systolic blood pressure, use of antihypertensive medication, and diabetes mellitus—attenuated the rate ratios to nonsignificant levels. A large proportion (96%) of the inverse association of serum magnesium with ischemic stroke incidence was explained by hypertension (systolic blood pressure and antihypertensive medication use) and diabetes status, when they were added to the regression model; hypertension and diabetes contributed almost equally to the attenuation of the magnesium association.

As shown in Table 4, there was a weak inverse association between dietary magnesium intake and ischemic stroke ($P_{trend} = 0.09$), and the association was essentially unchanged after adjustment for systolic blood pressure, use of antihypertensive medication, and diabetes mellitus. We further divided the lowest quartiles into 2 groups using the median value (quartile 1A, <12.5th percentile; quartile 1B, 12.5th–25th percentile). For serum magnesium, compared with participants in quartile 1A, age-, sex-, and race-adjusted rate ratios for those in the other groups were 0.63 (95% CI: 0.48, 0.84) for quartile 1B, 0.61 (95% CI: 0.47, 0.78) for quartile 2, 0.55 (95% CI: 0.42, 0.71) for quartile 3,

Table 3. Rate Ratios and 95% Confidence Intervals of Ischemic Stroke According to Serum Magnesium Levels, Atherosclerosis Risk in Communities Study, 1987–2004

	Quartiles of Serum Magnesium				P_{trend}
	1 (Low)	2	3	4 (High)	
No. at risk	3,619	3,529	3,431	2,974	
Median, mEq/L	1.44	1.60	1.70	1.84	
Ischemic stroke					
Person-years of follow-up	52,647	53,151	52,409	45,637	
No. of cases	199	142	123	112	
Incidence rate/1,000 person-years	3.8	2.7	2.3	2.5	
Rate ratios (95% confidence interval)					
Age, sex, and race adjusted	Referent	0.78 (0.62, 0.96)	0.70 (0.56, 0.88)	0.75 (0.59, 0.95)	0.005
Multivariate adjusted[a]		0.81 (0.65, 1.01)	0.75 (0.60, 0.95)	0.83 (0.65, 1.05)	0.05
Multivariate adjusted[b]		0.94 (0.75, 1.17)	0.90 (0.71, 1.13)	1.04 (0.82, 1.32)	0.99

[a] Adjusted for age, sex, race-field center, smoking status, body mass index, low density lipoprotein cholesterol, high density lipoprotein cholesterol, fibrinogen, von Willebrand factor, and educational level.
[b] Further adjusted for systolic blood pressure, use of antihypertensive medication, and diabetes mellitus.

and 0.58 (95% CI: 0.44, 0.77) for quartile 4 ($P_{trend} = 0.002$). For dietary magnesium, compared with participants in quartile 1A, age-, sex-, race-, and energy intake-adjusted rate ratios for those in the other groups were 1.12 (95% CI: 0.80, 1.57) for quartile 1B, 1.10 (95% CI: 0.81, 1.48) for quartile 2, 0.93 (95% CI: 0.66, 1.29) for quartile 3, and 0.83 (95% CI: 0.56, 1.24) for quartile 4 ($P_{trend} = 0.12$).

Furthermore, we analyzed the associations of serum and dietary magnesium with the incidence of ischemic stroke stratified by sex, race, antihypertensive medication use, diuretic use, hypertensive status, and diabetes status. There were no interactions between serum or dietary magnesium and sex, race, diuretic use, or diabetes status ($P_{interaction} > 0.10$) for ischemic stroke, whereas the inverse association of serum and dietary magnesium with the risk of ischemic stroke tended to be stronger in whites than blacks. For serum magnesium, compared with the lowest quartile, the age- and sex-adjusted rate ratios of ischemic stroke for the highest quartile were 0.70 (95% CI: 0.52, 0.95; $P_{trend} = 0.01$) for whites and 0.83 (95% CI: 0.56, 1.23; $P_{trend} = 0.13$) for blacks, and for dietary magnesium, the age-, sex-, and energy intake-adjusted rate ratios were 0.69 (95% CI: 0.45, 1.07; $P_{trend} = 0.02$) for whites and 1.01 (95% CI: 0.59, 1.73; $P_{trend} = 0.98$) for blacks.

Table 5 shows age-, sex-, race-, and energy intake-adjusted rate ratios of ischemic stroke according to combinations of

Table 4. Rate Ratios and 95% Confidence Intervals of Ischemic Stroke According to Dietary Magnesium Levels, Atherosclerosis Risk in Communities Study, 1987–2004

	Quartiles of Magnesium Intake				P_{trend}
	1 (Low)	2	3	4 (High)	
No. at risk	3,306	3,315	3,321	3,335	
Median, mg/day	152	213	271	362	
Ischemic stroke					
Person-years of follow-up	49,752	49,636	50,475	50,019	
No. of cases	140	154	134	131	
Incidence rate/1,000 person-years	2.8	3.1	2.7	2.6	
Rate ratios (95% confidence interval)					
Age, sex, race, and energy intake adjusted	Referent	1.03 (0.81, 1.31)	0.87 (0.66, 1.14)	0.78 (0.55, 1.09)	0.09
Multivariate adjusted[a]		1.09 (0.85, 1.38)	0.97 (0.74, 1.27)	0.89 (0.63, 1.25)	0.38
Multivariate adjusted[b]		1.08 (0.85, 1.37)	0.96 (0.73, 1.25)	0.80 (0.75, 1.13)	0.14

[a] Adjusted for age, sex, race-field center, smoking status, body mass index, low density lipoprotein cholesterol, high density lipoprotein cholesterol, fibrinogen, von Willebrand factor, educational level, and total energy intake.
[b] Further adjusted for systolic blood pressure, use of antihypertensive medication, and diabetes mellitus.

Table 5. Rate Ratios and 95% Confidence Intervals of Ischemic Stroke According to Combinations of Dietary and Serum Magnesium Levels, Atherosclerosis Risk in Communities Study, 1987–2004

	Combinations of Serum and Dietary Magnesium[a]			
	1	2	3	4
No. at risk	3,618	3,378	2,999	3,275
Ischemic stroke				
Person-years of follow-up	53,681	49,971	45,645	50,472
No. of cases	168	162	126	102
Incidence rate/1,000 person-years	3.1	3.2	2.8	2.0
Rate ratios (95% confidence interval)				
Age, sex, race, and energy intake adjusted	Referent	0.97 (0.75, 1.25)	0.98 (0.78, 1.24)	0.64 (0.48, 0.85)
Multivariate adjusted[b]		1.05 (0.81, 1.35)	1.05 (0.83, 1.32)	0.74 (0.56, 0.98)
Multivariate adjusted[c]		0.99 (0.76, 1.47)	1.16 (0.92, 1.47)	0.81 (0.61, 1.09)

[a] Median values of combinations: 1 (serum magnesium, ≤1.6 mEq/L; dietary magnesium, ≤241 mg/day); 2 (serum magnesium, ≤1.6 mEq/L; dietary magnesium, >241 mg/day); 3 (serum magnesium, >1.6 mEq/L; dietary magnesium, ≤241 mg/day); 4 (serum magnesium, >1.6 mEq/L; dietary magnesium, >241 mg/day).
[b] Adjusted for age, sex, race-field center, smoking status, body mass index, low density lipoprotein cholesterol, high density lipoprotein cholesterol, fibrinogen, von Willebrand factor, educational level, and total energy intake.
[c] Further adjusted for systolic blood pressure, use of antihypertensive medication, and diabetes mellitus.

dietary and serum magnesium levels. Compared with the group with less than median values of both dietary and serum magnesium, the group with both dietary and serum magnesium greater than the median had a significant lower risk of ischemic stroke (RR = 0.64, 95% CI: 0.48, 0.85), but not the groups with either dietary or serum magnesium below the median.

DISCUSSION

The main findings of this prospective study were that increased levels of serum magnesium were inversely associated with the incidence of ischemic stroke in a population-based sample of middle-aged men and women, although there was a weak association between dietary magnesium and the incidence of ischemic stroke. A previous study reported that low levels of serum magnesium predicted neurologic events, mainly ischemic stroke, in patients with advanced atherosclerosis (20), although that study was performed in a clinical setting and the sample size was relatively small ($n = 323$). Our results provide further evidence that serum magnesium levels could be inversely associated with the incidence of ischemic stroke in a large, biracial, population-based cohort and that the associations may be stronger among whites than blacks.

The mechanisms by which high serum magnesium levels decrease the risk of ischemic stroke have not been fully elucidated. Hypertension and diabetes mellitus could be mediators between serum magnesium and the incidence of ischemic stroke. In the present study, the inverse association of serum magnesium with the incidence of ischemic stroke was attenuated to a nonsignificant level after adjustment for hypertension and diabetes status, and the contribution of hypertension and diabetes status to the association between serum magnesium and ischemic stroke was more than 95%. Baseline serum magnesium was inversely associated with blood pressure and the prevalence of hypertension and diabetes mellitus (1). Further, these associations were also observed in prospective analyses (3, 7). On the other hand, previous experimental studies have shown that low plasma levels of magnesium accelerate atherogenesis by promoting inflammation and oxidative modification. Magnesium deficiency could be associated with the onset of an inflammatory response leading to increased circulating levels of cytokines, which trigger an oxidative response in endothelial cells (21, 22). Moreover, magnesium deficiency could be associated with the risk of thrombus formation. Platelet-dependent thrombosis was significantly increased in patients with stable coronary artery disease with low intracellular levels of magnesium (23). In the present study, serum magnesium levels were inversely associated with von Willebrand factor levels, and previous studies indicated that von Willebrand factor levels were positively associated with the incidence of ischemic stroke (16).

Dietary magnesium was marginally inversely associated with the incidence of ischemic stroke, and the association was weaker than that with serum magnesium. A prospective study of 43,738 US men reported that dietary magnesium was inversely associated with the risk of total stroke, although the association was stronger in hypertensive than normotensive men, and the association was attenuated to nonsignificant levels after adjustment for potassium and fiber intake (5). In the Nurses' Health Study, dietary magnesium was marginally inversely associated with increased risk of ischemic stroke (6), consistent with our findings. In the ARIC Study, the correlation coefficient between dietary and serum magnesium was weak, and there was no association of dietary magnesium with the incidence of

hypertension (7) or type 2 diabetes (3). In the present study, dietary magnesium intake was inversely associated with LDL cholesterol and positively associated with HDL cholesterol, but serum magnesium levels were positively associated with both LDL cholesterol and HDL cholesterol levels. Further, other dietary factors could reduce the risk of ischemic stroke, such as potassium and calcium intake (5, 6, 24, 25). These were positively associated with dietary magnesium intake but not with serum magnesium levels. Therefore, these discrepancies in the relations of dietary and serum magnesium with cardiovascular risk factors may explain, in part, the different associations of dietary and serum magnesium with incident ischemic stroke. On the other hand, compared with serum magnesium levels, the relatively less precise measurement of dietary magnesium intake could have resulted in a type 2 error. Unfortunately, the ARIC Study did not have information on supplemental magnesium intake, which could lead to underestimation of dietary magnesium intake. In addition, we did not examine the effect of magnesium supplementation on the associations of dietary and serum magnesium with incidence of ischemic stroke. Although validity and reliability studies of our food frequency questionnaire have been conducted previously (13), the validity and reliability of the assessment of dietary intake of magnesium are unknown. Measurement error typically would lead to an underestimation of the association of dietary magnesium with the incidence of ischemic stroke.

In the present study, compared with the group with less than median values of both dietary and serum magnesium, the group with both dietary and serum magnesium greater than the median had a 36% lower risk of ischemic stroke. This was not true for the groups with either dietary or serum magnesium below the median. To our knowledge, this is the first prospective study to report this joint association. Although many intervention trials using magnesium supplementation have been conducted to prevent hypertension, evidence of the effect of magnesium on blood pressure is inconsistent (26). It may be useful to monitor serum magnesium levels in a future intervention study by using magnesium supplementation.

Potential limitations of this study warrant consideration. First, we analyzed the associations between serum or dietary magnesium and ischemic stroke incidence using a single assessment of measurements at baseline, which may lead to misclassification of the habitual magnesium levels of some individuals. However, when we used the means of 2 visits to reanalyze the associations of serum and dietary magnesium with ischemic stroke incidence, the results were essentially unchanged. Second, serum magnesium accounts for less than 1% of the whole-body magnesium level (27). The serum magnesium level may not reflect magnesium levels accurately in other tissues, but the serum magnesium level has been shown to be correlated with the intracellular free magnesium level ($r = 0.54$) (28). Third, because treatment of hypertension with diuretics could lower the serum magnesium concentration (29), hypertension may be not only a mediator but also a confounder between serum magnesium and the incidence of ischemic stroke. In the present study, however, the inverse association of serum magnesium with the incidence of ischemic stroke was unchanged when we excluded participants using diuretics. Finally, although a large proportion of the inverse association of serum magnesium with ischemic stroke incidence was explained by hypertension and diabetes, other unmeasured factors related to hypertension and diabetes, such as inflammation, endothelial function, and insulin, may modify this conclusion.

In conclusion, low serum magnesium levels could be associated with the risk of ischemic stroke, in part, via the effects of hypertension and diabetes mellitus. Further study is needed to confirm the association of dietary or serum magnesium with hemorrhagic stroke in additional large prospective studies.

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